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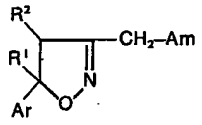
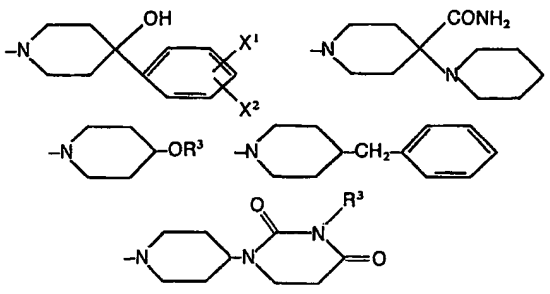
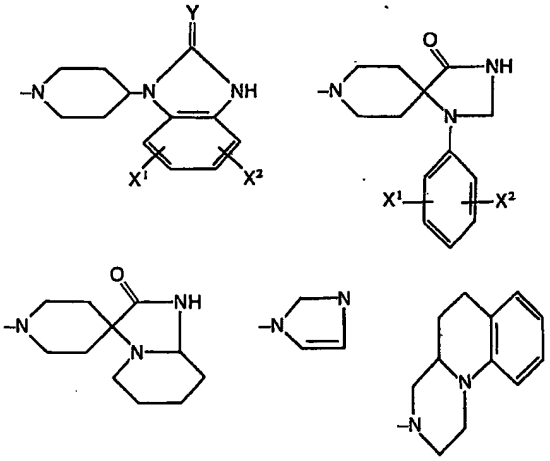
(54) ISOXAZOLE DERIVATIVES.

(57) Isoxazole derivatives represented by the following general formula:



[wherein Ar represents a phenyl or pyridyl group optionally substituted by halogen or lower alkoxy, R^1 represents a hydrogen atom, a lower alkyl group or a group of Ar, R^2 represents a hydrogen atom or, when R^1 and R^2 are taken together, they form a carbon-to-carbon bond, and Am represents an amine residue selected from the following:





wherein R^3 represents a hydrogen atom or a lower alkyl group, X^1 and X^2 each represent a hydrogen atom, a halogen atom or a trifluoromethyl group, and Y represents O or S] and the salts thereof. These are useful as psychotropic drugs and antimetics.

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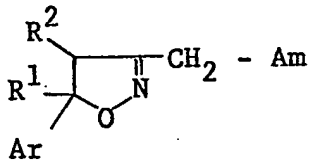
Specification

Isoxazole derivatives

Technical field and Disclosure of the Invention

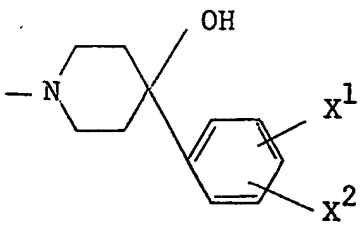
This invention relates to novel isoxazole derivatives having spontaneous locomotor suppressing activity, anti-apomorphine activity and like activity and useful as drugs such as psychotropic agent and antiemetic agent and represented by the general formula



(I)

and pharmaceutically acceptable acid addition salts thereof, and also to a process for preparing these compounds.

In the foregoing formula, Ar represents a phenyl group optionally containing a lower alkoxy group or a halogen atom as a substituent, or a pyridyl group, R^1 represents a hydrogen atom, a lower alkyl group or a group represented by Ar, R^2 represents a hydrogen atom or alternatively R^1 and R^2 are bound together and form a carbon-carbon bond, and Am represents an amino residue selected from the group consisting of the following residues: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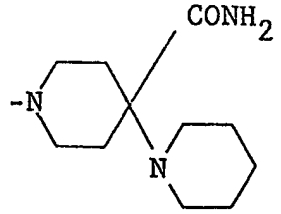
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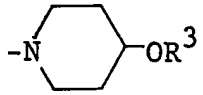
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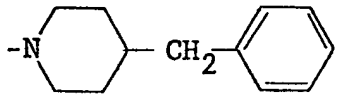
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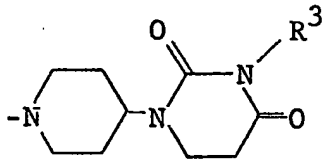
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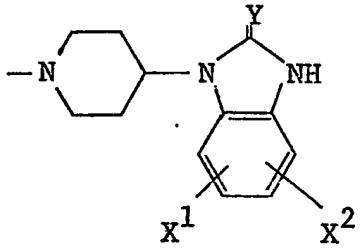
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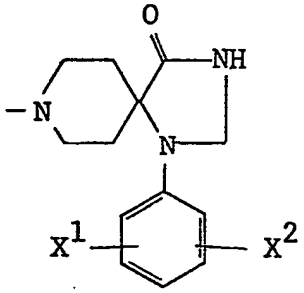
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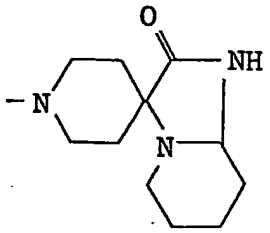
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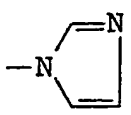
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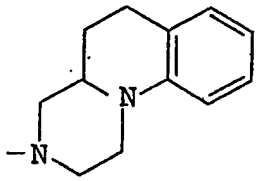
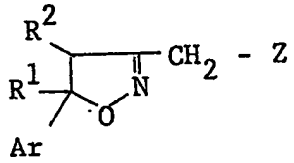


wherein R^3 represents a hydrogen atom or a lower alkyl group, X^1 and X^2 each represent a hydrogen atom, a halogen atom or a trifluoromethyl group, and Y represents O or S.

The term "halogen" herein includes fluorine, chlorine, bromine, etc. The term "lower alkoxy" herein represents a methoxy, ethoxy, propoxy, butoxy, etc. The term "lower alkyl" herein represents methyl, ethyl, propyl, butyl, etc.

The compounds of the formula (I) may be prepared by reacting a compound of the formula



(II)

wherein Ar, R^1 and R^2 are defined as above and Z represents a halogen atom or an organic sulfonyloxy group (e.g. tosyloxy, mesyloxy, etc.), with a compound of the formula

H - Am (III)

wherein Am is defined as above.

The reaction may be carried out usually in a solvent such as methanol, ethanol, isopropanol, benzene, toluene, xylene, dimethylformamide, chloroform, dichloroethane, acetone, methyl ethyl ketone, etc., at a temperature between room temperature and 140°C, preferably

between 50°C and 110°C, in the presence of potassium carbonate, sodium carbonate, triethylamine or like acid acceptor, for 1 to 48 hours, preferably 4 to 18 hours. The reaction may be accelerated by the use of a catalyst. Examples of such catalyst are potassium iodide, sodium iodide, etc.

The compound of the formula (I) may be converted into an acid addition salt. Typical examples of such an acid addition salt which is pharmaceutically acceptable are salts formed with use of hydrochloric acid, sulfuric acid, phosphoric acid, methanesulfonic acid, maleic acid, oxalic acid, succinic acid, fumaric acid, acetic acid, lactic acid and citric acid.

The experiments carried out for demonstrating anti-apomorphine activity of the compounds of this invention in mice will be described below.

Experimental method:

Groups of 5 male dd-mice (20-25 g body weight) each were used. Apomorphine hydrochloride (0.5 mg/kg) was subcutaneously administered 60 minutes after oral administration of test compound. Immediately after the apomorphine treatment, motor activity was determined for 20 minutes by animex. For the control groups, 0.5% methylcellulose solution was administered instead of test compound. The ED_{50}, a dose which inhibited the

motor activity by 50% as compared with the control, was determined.

Results:

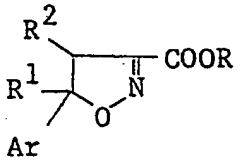
Compound	Anti-apomorphine activity ED_{50} (mg/kg, p.o.)
A	1.7
B	2.1
C	3.4
Clozapine	10

A: 1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(2-oxo-1-benzimidazolinyl)piperidine fumarate

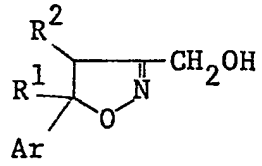
B: 1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(5-fluoro-2-oxo-1-benzimidazolinyl)-piperidine maleate

C: 1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(4-chlorophenyl)-4-hydroxypiperidine fumarate

The compounds of the formula (II) are novel and may be prepared, for example, by reducing a compound of the formula



wherein Ar, R^1 and R^2 are as defined above and R represents a lower alkyl group, with use of sodium borohydride etc., and reacting the resulting compound of the formula



wherein Ar, R^1 and R^2 are as defined above, with thionyl chloride, phosphorus tribromide or like halogenating agent or tosyl chloride, mesyl chloride or like organic sulfonating agent.

Reference Example 1

To a solution of 7 g of ethyl 5-phenyl-4,5-dihydroisoxazol-3-ylcarboxylate in 70 ml of methanol, cooled with ice, is added 1.5 g of sodium borohydride in small portions with stirring. After 4 hours has passed, the solvent is distilled off under reduced pressure and the residue is extracted with ethyl acetate. The extract is washed with water, dried and the solvent is evaporated. The crustalline residue thus obtained is recrystallized from isopropyl ether, giving 3-hydroxymethyl-5-phenyl-4,5-dihydroisoxazole in the form of white crystals.
Melting point : 73-74°C.

Reference Example 2

3-Hydroxymethyl-5-phenyl-4,5-dihydroisoxazole (3.2 g) is dissolved in 50 ml of anhydrous ether. To the solution cooled with ice is slowly added dropwise 2.6 g of thionyl chloride with stirring. The reaction mixture is allowed to stand overnight at room temperature and then the solvent is distilled off to give 3-chloromethyl-5-phenyl-4,5-dihydroisoxazole in the form of yellow brown oil.

The compounds of the formula (I) are used in combination with a suitable and conventional pharmaceutically acceptable excipient in the form of a pharmaceutical composition. The pharmaceutical composition may take usual forms such as of tablets, capsules, powders, granules, injection solutions, etc.

When administered for pharmaceutical uses, the compounds of this invention may, for example, be formulated into a pharmaceutical composition as follows.

Tablets (10 mg) may be prepared from the following ingredients:

Compound (I) or salt thereof	10 mg
Lactose	53 mg
Crystalline cellulose	15 mg
Corn starch	20 mg
Polyvinyl alcohol	1.5 mg
Magnesium stearate	0.5 mg
	100 mg

A compound (I) or salt thereof, crystalline cellulose and corn starch are mixed together and then the mixture is kneaded with 5% polyvinyl alcohol. The resulting mixture is granulated, dried and the dry granules are passed through 24-mesh screen. The fine granules are mixed with magnesium stearate to form granules for the preparation of tablets. Tablets are prepared by compressing the granules on punches (6.5 mm, 7.0R).

The dose of the compounds of the formula (I) ranges from 0.005 to 100 mg/kg body weight/day, preferably from 0.01 to 50 mg/kg body weight/day, which may be administered at one time or at several times, although variable depending on the age, body weight and/or severity of the conditions to be treated or response to the medication.

This invention will be better understood from the following examples, which are not to be construed as limitative of the present invention.

Example 1

3-Chloromethyl-5-phenyl-4,5-dihydroisoxazole (5.87 g), 6.3 g of 4-(4-chlorophenyl)-4-hydroxypiperidine, 4 g of potassium carbonate and 50 ml of ethanol are heated to 60-70°C with stirring for 6 hours. The reaction mixture is filtered and the filtrate is condensed by distillation under reduced pressure. To the residue are

added 200 ml of ethyl acetate and 100 ml of water. The organic layer is separated off, washed with water, dried on magnesium sulfate and evaporated under reduced pressure. The residue thus obtained is dissolved in isopropyl ether and alcoholic hydrochloric acid is added to the solution. The crystals thus formed is filtered and then recrystallized from isopropyl alcohol, giving 1-(5-phenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-(4-chlorophenyl)-4-hydroxypiperidine hydrochloride.

Melting point: 175-176°C (decomposition)

Example 2

3-Chloromethyl-5-(4-fluorophenyl)-4,5-dihydroisoxazole (40 g), 52 g of 4-(5-chloro-2-oxo-1-benzimidazolinyl)piperidine, 30 g of potassium carbonate, 15 g of potassium iodide and 1 liter of ethanol are heated to a temperature of 70 to 75°C with stirring for 48 hours. The reaction mixture is then filtered and the mother liquor is condensed under reduced pressure. To the residue are added 800 ml of chloroform and 500 ml of water and the mixture is stirred. The organic layer is separated off, washed with water and dried on magnesium sulfate, and the solvent is distilled off. To the resulting residue are added 130 ml of acetone and 100 ml of isopropyl ether. The crystals thus precipitated are filtered and recrystallized from a mixture of acetone

(400 ml) and isopropyl ether (450 ml), to give 67.5 g of 1-[5-(4-fluorophenyl)-4,5-dihydroxyisoxazol-3-ylmethyl]-4-(5-chloro-2-oxo-1-benzimidazolinyl)piperidine having a melting point of 163 to 164°C. Hydrochloride of this compound melts at 216°C (decomposition).

A 46.5 g-quantity of the above compound (free base) is dissolved in 200 ml of ethanol, and a solution of 15 g of L-tartaric acid in 200 ml of water is added to the ethanol solution. The resulting mixture is allowed to stand at room temperature. The crystals thus precipitated is recrystallized three times from ethanol-water (6:4) to give tartrate monohydrate as colorless prisms. The tartrate monohydrate is treated with an aqueous solution of sodium bicarbonate to give (-)-1-[5-(4-fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(5-chloro-2-oxo-1-benzimidazolinyl)piperidine. Melting point: 143-145°C. $[\alpha]_D^{25}$: - 108.8 (chloroform).

The (+)-isomer of the above compound is obtained in the same manner as above with use of D-tartaric acid. Melting point: 142-144°C. $[\alpha]_D^{25}$: + 112.6 (chloroform).

Example 3

3-Chloromethyl-5-(4-fluorophenyl-4,5-dihydroisoxazole (3.2 g), 3.5 g of 4-oxo-1-phenyl-1,3,8-triazaspiro[4,5]decane, 2.1 g of potassium carbonate and

100 ml of ethanol are refluxed for 7.5 hours with stirring. The resulting reaction mixture is filtered and the mother liquor is concentrated. To the residue obtained is added 100 ml of water and the mixture is extracted with ethyl acetate. The extract is washed with water and dried on magnesium sulfate and the solvent is distilled off under reduced pressure. The resulting residue is dissolved in a small amount of alcohol and alcoholic hydrochloric acid is added to the solution. The crystals thus precipitated are filtered and recrystallized from methanol to give 5-(4-fluorophenyl)-3-(4-oxo-1-phenyl-1,3,8-triazaspiro[4,5]decan-8-ylmethyl)-4,5-dihydroisoxazole hydrochloride. Melting point: 219°C (decomposition).

The following compounds may be prepared in the same manner as in the preceding Examples.

° 1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(4-chlorophenyl)-4-hydroxypiperidine

Melting point of 1/2 fumarate: 147-148°C

° 1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(2-oxo-1-benzimidazolinyl)piperidine

Melting point of fumarate: 206°C (decomp.)

° 1-[5-(2-Chlorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(5-chloro-2-oxo-1-benzimidazolinyl)piperidine

Melting point of hydrochloride: 244°C (decomp.)

° 1-[5-(3-Chlorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(5-chloro-2-oxo-1-benzimidazolinyl)piperidine

Melting point of maleate: 197°C (decomp.)

° 1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(5-fluoro-2-oxo-1-benzimidazolinyl)piperidine

Melting point of maleate: 201°C (decomp.)

° 1-[5-(4-Fluorophenyl)-4,5-dihydroisoxaxol-3-ylmethyl]-4-carbamoyl-4-piperidino-piperidine

Melting point of dihydrochloride: 234°C (decomp.)

° 1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-benzylpiperidine

Melting point of hydrochloride: 184°C

° 1-(5-Methyl-5-phenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-(5-chloro-2-oxo-1-benzimidazolinyl)piperidine

Melting point of maleate: 218°C (decomp.)

° 5-Phenyl-3-[4-oxo-1-(4-bromophenyl)-1,3,8-triazaspiro-[4,5]-decan-8-ylmethyl]-4,5-dihydroisoxazole

Melting point of maleate: 221°C (decomp.)

° 1-(5-Phenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-hydroxypiperidine

Melting point of maleate: 115-119°C

° 1'-(5-Phenyl-4,5-dihydroisoxazol-3-ylmethyl)-1,2,3,5,6,7,8,8a-octahydro-2-oxoimidazo[1,2-a]-pyridine-3-spiro-4'-piperidine

Melting point of dihydrochloride: 223°C (decomp.)

° 1-[5-(4-Chlorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(5-chloro-2-oxo-1-benzimidazolinyl)piperidine

Melting point of hydrochloride: 230°C (decomp.)

° 1-[5-(4-Methoxyphenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(5-chloro-2-oxo-1-benzimidazolinyl)piperidine

Melting point of hydrochloride: 229°C (decomp.)

° 1-(5-Phenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-(5-chloro-2-thioxo-1-benzimidazolinyl)piperidine

Melting point of 1/2 fumarate: 208-209°C

° 1-(5-Phenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-methoxypiperidine

Melting point of hydrochloride: 162-164°C

° 1-(5-Phenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-carbamoyl-4-piperidino-piperidine

Melting point of dihydrochloride: 158°C (decomp.)

° 1-(5-Phenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-benzylpiperidine

Melting point of hydrochloride: 208°C (decomp.)

° 1-(5-Phenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-(2-oxo-1-benzimidazolinyl)piperidine

Melting point of fumarate: 206°C (decomp.)

° 1-[5-(2-Pyridyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(5-chloro-2-oxo-1-benzimidazolinyl)piperidine

Melting point of maleate: 188°C

° 1-(5-Phenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-(5-fluoro-2-oxo-1-benzimidazolinyl)piperidine

Melting point of hydrochloride: 229°C (decomp.)

° 5-(Phenyl-3-(4-oxo-1-phenyl-1,3,8-triazaspiro[4,5]-decan-8-ylmethyl)-4,5-dihydroisoxazole

Melting point of hydrochloride: 226°C (decomp.)

° 1-(5-Phenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-(5-chloro-2-oxo-1-benzimidazolinyl)piperidine

Melting point of maleate: 204°C (decomp.)

° 1-(5-Phenyl-3-isoxazolinylmethyl)-4-(5-chloro-2-oxo-1-benzimidazolinyl)piperidine

Melting point of hydrochloride: 250°C (decomp.)

° 1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-imidazole

Melting point of fumarate: 110-111°C

° 1-[5-(2-Pyridyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(3-methyl-2,4-dioxo-1-hexahydropyrimidinyl)piperidine

Melting point of maleate: 169°C (decomp.)

° 1-(5,5-Diphenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-(5-chloro-2-oxo-1-benzimidazolinyl)piperidine

° 1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(2-thioxo-1-benzimidazolinyl)piperidine

Melting point of fumarate: 125°C (decomp.)

° 1-(5,5-Diphenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-(2-thioxo-1-benzimidazolinyl)piperidine

- 1-(5,5-Diphenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-(2-oxo-1-benzimidazolinyl)piperidine

  Melting point: 197-199°C

- 1-(5,5-Diphenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-(5-fluoro-2-oxo-1-benzimidazolinyl)piperidine
- 1-(5,5-Diphenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-hydroxy-4-(4-chlorophenyl)piperidine

  Melting point: 153-154°C

- 1-[5,5-Bis(4-fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(5-chloro-2-oxo-1-benzimidazolinyl)-piperidine

  Melting point: 199-200°C

- 1-[5,5-Bis(4-fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(2-thioxo-1-benzimidazolinyl)piperidine
- 1-[5,5-Bis(4-fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(2-oxo-1-benzimidazolinyl)piperidine
- 1-[5,5-Bis(4-fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(5-fluoro-2-oxo-1-benzimidazolinyl)-piperidine
- 1-[5,5-Bis(4-fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-hydroxy-4-(4-chlorophenyl)piperidine

  Melting point: 163-164°C

- 1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(4-chloro-3-trifluoromethylphenyl)-4-hydroxypiperidine

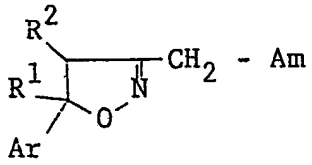
° 3-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-2,3,4,4a,5,6-hexahydro-1H-pyrazino-[1,2-a]-quinoline

Melting point of oxalate: 148°C (decomp.)

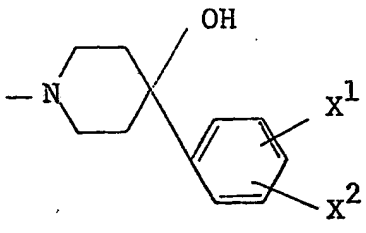
While the invention has been described in detail and with reference to specific embodiments thereof, it is apparent that various alterations and modifications can be made without departing from the spirit and scope thereof.

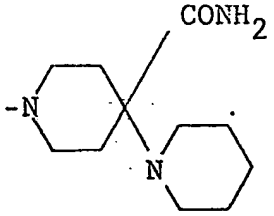
CLAIMS:

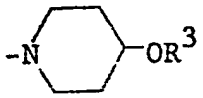
1. An isoxazole derivative represented by the formula

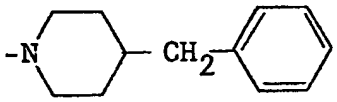


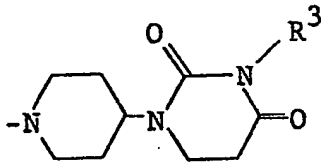
or salts thereof wherein Ar represents a phenyl group which may optionally be substituted with a halogen atom or a lower alkoxy group, or a pyridyl group R^1 represents a hydrogen atom, a lower alkyl or a group represented by a group Ar, R^2 represents a hydrogen atom, or alternatively R^1 and R^2 are bound together and form a carbon-carbon bond, and Am represents an amino residue selected from the group consistinf of the following residues:

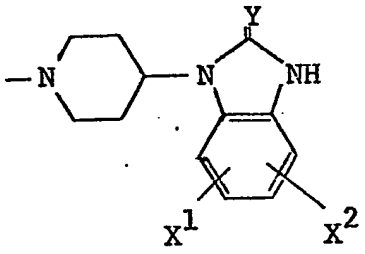

OH
N
X1
X2
,

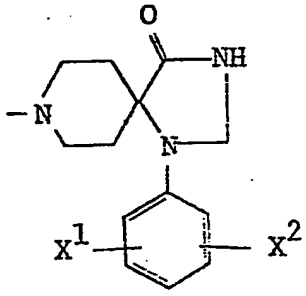

CONH2
N
N
,

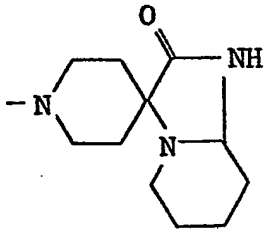

N
OR3
,

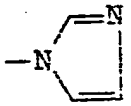

N
CH2
,

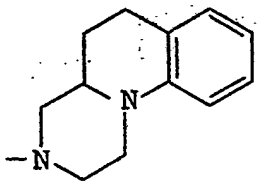

O
R3
N
N
O
,


Y
N
NH
X1
X2
,


O
NH
N
N
X1
X2
,


O
NH
N
N
,


N
N
and


N
N

wherein R^3 represents a hydrogen atom or a lower alkyl group, X^1 and X^2 each represent a hydrogen atom, a halogen atom or a trifluoromethyl group and Y represents O or S.

2. The compound of claim 1: 1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(5-chloro-2-oxo-1-benzimidazolinyl)piperidine.

3. The compound of claim 1: 1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(2-oxo-1-benzimidazolinyl)piperidine.

4. The compound of claim 1: 1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(5-fluoro-2-oxo-1-benzimidazolinyl)piperidine.

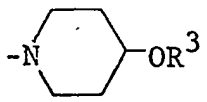
5. The compound of claim 1: 1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(4-chlorophenyl)-4-hydroxypiperidine.

6. The compound of claim 1: 5-(4-Fluorophenyl)-3-(4-oxo-1-phenyl-1,3,8-triazaspiro-[4,5]-decan-8-ylmethyl)-4,5-dihydroisoxazole.

7. The compound of claim 1: 1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(2-thioxo-1-benzimidazolinyl)piperidine.

8. The compound of claim 1: 1-(5-Phenyl-4,5-dihydroisoxazol-3-ylmethyl-4-(5-chloro-2-thioxo-1-benzimidazolinyl)piperidine.

9. A pharmaceutical composition comrpising a compound of claim 1 and a pharmaceutically acceptable excipient.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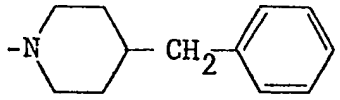
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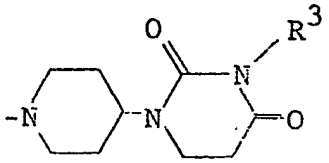
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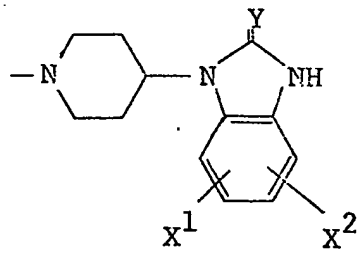
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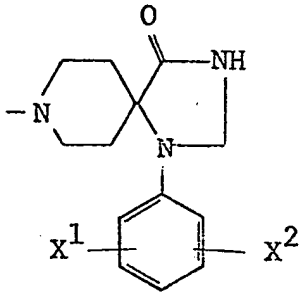
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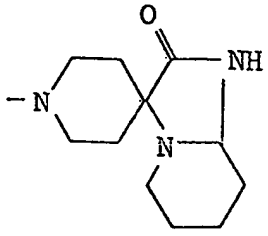
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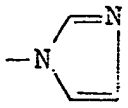
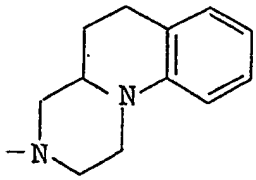

and


These compounds are useful as drugs such as psychotropic agent and antiemetic agent.

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP80/00286

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [8]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl.[3] C07D 413/06, C07D 413/14, C07D 471/04, C07D 471/10, C07D 471/20

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
I P C	C07D 413/06, C07D 413/14, C07D 471/04 C07D 471/10, C07D 471/20, C07D 211/10 C07D 211/44, A61K 31/42, A61K31/495

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X	DT, A, 2245971, 1974-3-14	1 - 9
X	JP, A, 49-24973, 1974-3-5 P 1 - 5	1 - 9
X	US, A, 4133889, 1979-1-9	1 - 9

* Special categories of cited documents: [15]

"A" document defining the general state of the art

"E" earlier document but published on or after the international filing date

"L" document cited for special reason other than those referred to in the other categories

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but on or after the priority date claimed

"T" later document published on or after the international filing date or priority date and not in conflict with the application, but cited to understand the principle or theory underlying the invention

"X" document of particular relevance

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
February 20, 1981 (20.02.81)	March 2, 1981 (02.03.81)
International Searching Authority [1]	**Signature of Authorized Officer [20]**
Japanese Patent Office	